REMARKS

Claims 1-13 and 19-24 are currently pending. Claims1, 5, and 10 are currently amended. Claims 14-18 and 25-43 are currently withdrawn. Claims 2-4 and 44-76 have been cancelled. Applicants thank the Examiner for pointing out the misnumbering of claims.

Response to Restriction Requirement

Election of Invention

Applicants hereby elect Invention I, Claims 1-42, for examination. Applicants reserve the right to pursue claims to nonelected subject matter in divisional patent applications.

Election of disease:

Election of a disease recited in any of Claims 12-18 was required, on the grounds that the recited diseases allegedly have separate symptoms, mechanisms, and etiologies (Office Action (OA) page 4, lines 9-17). It was noted that this election is not a species election. Although Applicants disagree with this requirement because the Examiner has not provided any evidence showing that separate mechanisms and etiologies of the recited diseases precludes screening a subject as claimed herein, Applicants nonetheless elect Alzheimer's disease, as recited in Claim 13, in order to facilitate prosecution of the present application.

Election of species:

Election of a species of tissue was required, on the grounds that the tissues on which the claimed invention is to be practiced are patentably distinct species of tissues. Applicants elect brain tissue, with traverse. Claims 1-23 read on the elected species.

Applicants traverse the species election requirement on the grounds that the specification teaches that BMAA can be measured not only in brain tissue, but also in skin samples (Example 2 and Table 2). Further, Exhibit 1 (Declaration of Dr. Sandra Banack) and Exhibit 2 (Table of BMAA Levels in Hair Samples) submitted herewith, disclose measurement of BMAA in hair samples from living subjects. Therefore, Applicants submit that the species election requirement is improper and request that it be withdrawn. Applicants request that Claims 25-43 be examined.

Claim Rejections Under 35 U.S.C. §112

Claim Rejections Under 35 U.S.C. §112, first paragraph

Claims 1-11 and 19-24

Claims 1-11 and 19-24 stand rejected under 35 U.S.C. §112, first paragraph, on the grounds that the specification, while being enabling for a method of screening for the presence of BMAA in patients who have Alzheimer's disease, allegedly does not reasonably provide enablement for any other neurological diseases. Applicants respectfully disagree.

First, Applicants point out that the specification teaches that measurable levels of BMAA have been observed in patients having two different diseases: ALS-PDC in Chamorros, and Alzheimer's disease in Canadian patients (Table 3). Further, Exhibit 1 (Declaration of Dr. Sandra Banack) and Exhibit 2 (Table of BMAA Levels in Hair Samples), submitted herewith, disclose that detectable levels of BMAA were found in hair samples from living patients having clinical diagnoses of neurological disorders including Alzheimer's disease, Alzheimer's type dementia, pre-Alzheimer's vascular dementia, or dementia. Therefore, Applicants conclude that the specification is enabling for other neurological diseases, and respectfully request that the rejection of Claims 1-11 and 19-24 under 35 U.S.C. §112, first paragraph be withdrawn.

Claims 19-21

Claims 19-21 stand rejected under 35 U.S.C. §112, first paragraph, on the grounds that the samples described in Table 3 of the specification are "necessarily retrospective" such that it is allegedly "impossible" to know if data obtained from living subjects could be used in a forward-looking manner, to determine likelihood, latency to onset, or severity of the neurological disorder. Applicants respectfully disagree.

The disclosure in the specification enables one of skill in the art to make and use the invention of Claims 19-21 as required by 35 U.S.C. §112, first paragraph, on page 12, beginning on line 11 at line 24, to page 14, line 2, and throughout the specification. Non-limiting examples of the methods taught in the specification include, repeated testing to generate time series data, correlating the levels of a neurotoxic amino acid in tissue samples with other determinations relevant to assessing neurological disorders, measuring neurotoxic amino acid levels in asymptomatic individuals, and correlating neurotoxic amino acid levels with severity of a neurological disorder.

Further, Exhibit 1 (Declaration of Dr. Sandra Banack) and Exhibit 2 (Table of BMAA Levels in Hair Samples), submitted herewith, disclose that detectable levels of BMAA were found in hair samples from living patients having clinical diagnoses of neurological disorders

including Alzheimer's disease, Alzheimer's type dementia, pre-Alzheimer's vascular dementia, or dementia, while hair samples from "control" subjects that did not have clinical diagnoses of neurological disorders, did not have detected levels of BMAA. Therefore, Applicants submit that the specification teaches one of skill in the art how to practice the invention of Claims 19-21 and therefore request that this rejection be withdrawn.

Claim Rejections Under 35 U.S.C. §112, second paragraph

Claims 5 and 6 stand rejected under 35 U.S.C. §112, second paragraph, on grounds that the term "protein-bound BMAA" is allegedly vague and indefinite. It is suggested that the claim be amended to read "BMAA incorporated into protein." Applicants respectfully traverse.

According to the MPEP, "[w]hen the specification states the meaning that a term in the claim is intended to have, the claim is examined using that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art." (*In re Zletz*, 893 F.2d 319, 12 USPQ2d 1320 (Fed. Cir. 1989), cited at MPEP §2173.05(a)). In the present application, the specification discloses "protein-bound forms of neurotoxic amino acids or neurotoxic derivatives thereof associated with neurological disorders (*e.g.*, bound to proteins or incorporated into proteins)" (Specification page 10, lines 13-15), and further discloses that "BMAA . . . can exist in a protein-bound form, where it may be incorporated into a protein or it may be otherwise associated with a protein." (Specification page 10, lines 21-22). Because the meaning of the term "protein-bound BMAA" in Claim 5 is apparent from the specification at the time the application was filed, Claims 5 and 6 comply with the requirements of 35 U.S.C. §112, second paragraph and the rejection should be withdrawn.

Claim Rejections Under 35 U.S.C. §102

Rejection of Claims 1, 2, 7-13, 22 and 23 over Ellison et al. and Martinez et al.

Claims 1, 2, 7-13, 22 and 23 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by both Ellison *et al.* (1986, *Ann Neurol* 20:616-621) and Martinez *et al.* (1993, *J Neural Transm Park Dis Dement Sect* 6:1-9). Claim 24 also stands rejected under 35 U.S.C. §102(b) as allegedly anticipated by Ellison *et al.*

According to the Office Action, Ellison *et al.* "teach the measurement of glutamate, which is a neurotoxic amino acid" (OA page 9, lines 12-13) and Martinez *et al.* "teach that glutamate levels are significantly altered in cerebrospinal fluid taken from patients with Alzheimer-type dementia" (OA page 9, lines 21-22). Claim 1 has been amended to recite BMAA or a BMAA derivative, thereby rendering this rejection moot.

Rejection of Claims 1-4, 7-13, and 22-24 over Kisby et al.

Claims 1-4, 7-13, and 22-24 stand rejected under 35 U.S.C. 102(b) as allegedly anticipated by Kisby *et al.* (1988, *J Neurosci Meth* 26:45-54), on the grounds that Kisby *et al.* teach an HPLC-based method of detecting BMAA in neural tissue in rats and monkeys, and further on the basis of the assertion that "Kisby *et al.* explicitly contemplated the use of this method 'to determine the role of BMAA in the Western Pacific amyotrophic lateral sclerosis/Parkinson-dementia complex for which cycad seed is the principal etiological candidate'." (OA page 9, lines 30-32, quoting Kisby *et al.*, final sentence of abstract).

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1052 (Fed. Cir. 1987), cited at MPEP §2131. Kisby *et al.* does not disclose Alzheimer's disease. However, it is argued that "the method of detection devised by Kisby *et al.* to be used in the determination of BMAA levels in ALS-PD, is inherently a method for the detection of Alzheimer's disease." (OA, page 10, lines 11-13) and "the monkeys used by Kisby *et al.* in developing their method had a form of Alzheimer's disease" (OA page 10, lines 28-29). Therefore, the present rejection of claims as inherently anticipated by Kisby *et al.*, is premised on the Examiner's statement that "[t]his disease, ALS-PDC, is a form of Alzheimer's disease" (OA, page 10, lines 1-2).

According to the MPEP, extra references or evidence can be used to show that a characteristic not disclosed in the primary reference is inherent, but "[s]uch evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA v. Monsanto Co.*, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) cited at MPEP §2131.01, III. Here, the additional references do not "make clear that the missing descriptive matter" with respect to Alzheimer's disease is "necessarily present in the thing described" in the Kisby *et al.* reference. In fact, the additional references cited in the Office Action teach away from characterizing ALS-PDC as a form of Alzheimer's disease. Therefore, the additional references cannot be relied upon to argue that Kisby *et al.* inherently discloses Alzheimer's disease and therefore, the rejection under 35 U.S.C. §102(b) over Kisby *et al.* is improper and should be withdrawn.

ALS-PDC is not a form of Alzheimer's

The references cited in the Office Action do not support the statement that "[t]his disease, ALS-PDC, is a form of Alzheimer's disease." The Brownson *et al.* reference (2002, *J Ethnopharmacol* 82:159-167) states that "ALS-PDC is a complex of amyotrophic lateral

sclerosis and parkinsonism dementia complex with additional symptoms of Alzheimer's" (Brownson *et al.*, Abstract, lines 4-5). The Brownson *et al.* text cited by the Examiner (OA page 10, lines 3-4, citing Brownson *et al.* page 160, lines 2-4) occurs within a discussion of the variety of symptoms seen in Chamorros [*i.e.*, ALS-PDC patients], where some patients manifest signs of parkinsonism, while others exhibit limb weakness common with ALS, and "[s]till other patients develop cognitive dysfunction typical of dementia found in Alzheimer's" (Brownson *et al.*, page 159, left column, last sentence, to page 160, line 4). Applicants conclude that the disclosure in Brownson *et al.* teaches away from characterizing ALS-PDC as a form of Alzheimer's disease, by describing the variety of symptoms, including non-Alzheimer's symptoms, seen in ALS-PDC patients.

The Spencer *et al.* reference (1987, *Science* 237:517-522) refers to "Alzheimer-type dementia" (abstract, line 2) as one aspect of "this disease" which Spencer *et al.* describe in the text as a parkinsonism-dementia (PD) clinical variant of amyotrophic lateral sclerosis (ALS), or ALS-PD (Spencer *et al.*, page 517, left column, first paragraph). The text cited by the Examiner (OA page 10, lines 4-5, citing Spencer *et al.*, page 519, final paragraph) likewise refers to various neuropathologies observed in human ALS-PD including "Alzheimer-type" neuropathology. Applicants conclude that the disclosure in Spencer *et al.* does not characterize ALS-PD as a form of Alzheimer's and in fact, teaches away from such a characterization by describing ALS-PD as a clinical variant of ALS.

Applicants are unable to find where in the Lewin reference (1987, *Science* 237:483-484), "Lewin presented the link between BMAA and Alzheimer's disease as a fact" as asserted by the Examiner (OA page 10, lines 5-6). The Lewin reference is a commentary on the Spencer *et al.* research paper discussed above. In the text cited by the Examiner – Lewin, page 484, left-hand column, last full paragraph— Lewin uses the same term as Spencer *et al.*, namely, "Alzheimer's-like dementia," to describe one aspect of the disease which Spencer *et al.* described as a clinical variant of ALS (Spencer *et al.*, page 517, left column, first paragraph). Applicants conclude that Lewin does not teach what is asserted in the Office Action.

The Forman *et al.* reference (2002, *Am Jnl Pathology* 160:1725-1731) notes that ALS-PDC is characterized by neuropathological changes, including neurofibrillary tangles (NFTs) that are "similar both biochemically and immunohistochemically to that observed in Alzheimer's disease (AD)" (page 1725, right column, lines 1-7, 7-17), but also discloses:

> "[h]owever, ALS/PDC is distinguished from AD by the laminar distribution of these NFTs, the prominent glial pathology in ALS-PDC including granular

> hazy astrocytic inclusions, and well as the absence of amyloid plaques in most, but not all, cases." " (page 1725, right column, lines 14-1, reference citations removed, emphasis added).

Similarly, the Forman *et al.* text cited by the Examiner (Forman *et al.*, page 1730, paragraph beginning at the end of the first column, cited at OA page 10 at line 10) points out differences between Alzheimer's disease (AD) and Guam PDC, as well as similarities. Applicants conclude that the disclosure in Forman *et al.* teaches away from characterizing ALS-PDC as a form of Alzheimer's disease by clearly and distinctly listing differences that allow the two diseases to be distinguished.

As noted above, Kisby *et al.* is silent about Alzheimer's disease and therefore, additional references were cited to support the proposition that ALS-PDC is allegedly a form of Alzheimer's disease and therefore, Kisby *et al.* inherently disclosed Alzheimer's disease. For the reasons presented above, the additional references (Brownson *et al.*, Spencer *et al.*, Lewin, and Forman *et al.*) do not characterize ALS-PDC as a form of Alzheimer's disease and in fact, they teach away from such a characterization. These references do not "make clear that the missing descriptive matter is necessarily present in the thing described in the reference" (*Continental Can* at 1749, cited at MPEP §2131.01, III), *i.e.*, the references do not show that Kisby *et al.* inherently disclosed Alzheimer's disease. Because the Kisby *et al.* reference does not "expressly or inherently" disclose Alzheimer's disease, Kisby *et al.* does not anticipate the claimed subject matter. Therefore, the rejection of Claims 1-4, 7-13, and 22-24 under 35 U.S.C. §102(b) over Kisby *et al.* is improper and should be withdrawn.

Claim Rejections Under 35 U.S.C. §103

Claims 5 and 6 stand rejected under 35 U.S.C. §103 as allegedly unpatentable over Kisby *et al.* (1988, *J Neurosci Meth* 26:45-54), in view of Duncan *et al.* (1990, *Neurology* 40:767-772) and Duncan *et al.* (1992, *J Neuroscience*, 12:1523-1537). Kisby *et al.* allegedly teach a method of detecting BMAA in brain tissue and contemplate its use in studying ALS-PD, but do not teach analyzing the amount of BMAA bound to protein (OA page 11, lines 13-15), while Duncan *et al.* (1990, 1992) allegedly teach acid hydrolysis of BMAA-containing proteinaceous samples in a method that detects both free and conjugated BMAA. It is stated that, "[f]or purposes of this rejection, 'protein-bound BMAA' is interpreted as meaning BMAA that can be released from protein by acid hydrolysis." (OA, page 11, lines 11-12) It is argued that, "[s]ince BMAA is a modified amino acid, proteins are made of amino acids, and proteins can be degraded into their constituent amino acids by hydrolysis,

one of ordinary skill in the art would have expected combining these two methods to be successful in releasing protein-bound BMAA." (OA page 12, lines 1-4) Applicants traverse this rejection for the reasons presented below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See*, MPEP §§ 2142, 2143. Here, the combination of cited references does not teach all the claim limitations. Because a criterion for a *prima facie* case of obviousness has not been satisfied, no *prima facie* case of obviousness has been established and therefore, the rejection of Claims 5 and 6 under 35 U.S.C. §103(a) is improper and should be withdrawn.

The combination of references do not teach or suggest all the claim limitations

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka* 180 USPQ 580 (CCPA 1974). In the present case, the cited combination of references does not teach analysis of protein-bound BMAA as claimed herein.

It is admitted that Kisby *et al.*, the primary reference, "do not teach analyzing the amount of BMAA bound to protein" (OA page 11, lines 14-16), so Duncan *et al.* (1990, 1992), the secondary references, are asserted as allegedly disclosing release of protein-bound BMAA. Applicants traverse the argument that the method of Duncan *et al.* (1990, 1992), "uses a similar mechanism (hydrolysis) to release large amount [*sic*] of BMAA from proteinaceous samples" (OA page 11, lines 30-31.

Duncan *et al.* (1992) describe "total" BMAA as "free + conjugated" BMAA in their samples. In contrast, Applicants disclose that methods of the invention include analysis of free, protein-bound, or conjugated forms of neurotoxic amino acids or neurotoxic derivatives, where protein-bound BMAA may be incorporated into a protein or may be otherwise associated with a protein. (Specification page 10, lines 11-16 and lines 20-22). Therefore, Duncan *et al.* (1990, 1992) do not teach or suggest analysis of protein-bound BMAA.

Further, Applicants submit that the rejection of Claims 5 and 6 over Duncan *et al.* is improper because the statement that "[f]or purposes of this rejection, 'protein-bound BMAA' is interpreted as meaning BMAA that can be released from protein by acid hydrolysis." (OA, page 11, lines 11-12) was erroneously applied to the method disclosed in Duncan *et al.* (1990, 1992). This erroneous interpreation was relied upo to argue that, "[s]ince BMAA is a

modified amino acid, proteins are made of amino acids, and proteins can be degraded into their constituent amino acids by hydrolysis, one of ordinary skill in the art would have expected combining these two methods to be successful in releasing protein-bound BMAA." (OA page 12, lines 1-4) Applicants submit that the burden is on the Examiner to provide support for this conclusion. MPEP §2144.03.

Applicants point out that the method of Duncan *et al.* (1990, 1992; more extensively described in Duncan, 1990, page 768, right column) disclosed extracting samples by continuous shaking with 0.1 M HCl for up to 72 hours, after which the residual solid matter was centrifuged, the supernatant was collected, and BMAA in the supernatant was measured. That is, Duncan *et al.* only measured BMAA in the fraction containing materials are soluble in 0.1M HCl. In contrast, the Applicants disclose that tissues were homogenized in 0.1 N trichloroacetic acid and centrifuged to precipitate proteins and extract free amino acids (page 38, lines 15-16), and protein-bound BMAA in the precipitate was released by hydrolysis at 110° C in constant boiling 6N HCl for 24 hours (page 38, lines 16-17). Duncan *et al.* do not teach or suggest extracting BMAA from the precipitate in boiling concentrated acid (*e.g.*, 6N HCl). In light of the differences between the method of Duncan *et al.* and the method disclosed in the specification, the Examiner must provide evidence to support the conclusion that the method of Duncan *et al.* degrades proteins into their constituent amino acids by hydrolysis and releases protein-bound BMAA.

Because a basic criterion for a *prima facie* case of obviousness has not been satisfied, *i.e.*, the cited references fail to teach or suggest all the claim limitations, a *prima facie* case of obvious has not been established and therefore, the rejection of Claims 5 and 6 under 35 U.S.C. §103(a) is improper and should be withdrawn.

CONCLUSION

Claims 1-13 and 19-24 are currently pending. Claims1, 5, and 10 are currently amended. Claims 14-18 and 25-43 are currently withdrawn. Claims 2-4 and 44-76 have been cancelled. Applicants submit that, in light of the amendments and remarks presented herein, the claims are now in condition for allowance.

Applicants believes that fees are due. Please charge any fees associated with the submission of this paper to Deposit Account Number 502212. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

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